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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/449,077	11/24/1999	Dr. Thomas Hunig	12254/	5838

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EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	

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26

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/449077	Applicant(s) HUNICE
	Examiner GAMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on ~~RAN~~ 4/18/03

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _____ is/are pending in the application. 1-41

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 5-12, 16-23, 25-40

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected. 1-4, 13-15, 24, 41-42

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 4/18/03 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 26

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644, Technology Center 1600.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed 4/28/03 (Paper No. 24), has been entered.

Applicant's amendment filed 4/28/03 (Paper No. 25), has been entered.
Claims 41-42 have been added.

Claims 1-4, 13-15, 24 and 41-42 are being acted upon as the elected invention.

Claims 5-12, 16-23 and 25-40 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

3. Formal drawings submitted 3/5/03 (Paper No. 22), comply with 37 CFR 1.84.

4. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(d) Brief Summary of the Invention.
(e) Brief Description of the Several Views of the Drawing(s).
(f) Detailed Description of the Invention.
(g) Claim or Claims (commencing on a separate sheet).
(h) Abstract of the Disclosure (commencing on a separate sheet).
(i) Drawings.

Once again, applicant is requested to minimally provid the appropriate headers for the various sections found in the instant specification.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 2(b) is objected to in that "pursuant" should be spelled "pursuant".

6. Claims 1-4, 13-15, 24 and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 13-15, 24, 41-42 are indefinite in the recitation of "human-compatible monoclonal antibody" because the metes and bounds are ambiguous and ill-defined. Pages 2-3, overlapping paragraph, of the instant specification discloses "monoclonal antibodies in accordance with the invention are therefore human-compatible on the one hand, be it per se or by humanisation". However, it is not clear how a monoclonal antibody is "per se" a "human-compatible" monoclonal antibody in the absence of "humanization".

As pointed out previously, the recitation of "monoclonal antibody" in the dependent claims leads to confusion concerning the metes and bounds of recitation of "human-compatible" monoclonal antibody. Further, the dependent claims recite "optionally, humanization" (e.g. see claims 2(b)), as well as other method steps, which result in simply providing monoclonal antibodies in the absence of humanization procedures as product-by-process limitations, that is, the resultant claimed antibodies are simply mouse anti-CD28 antibodies and not "human-compatible anti-CD28 antibodies. Such monoclonal antibodies are not or would not be expected to be "human-compatible". The claimed hybridoma cells produce mouse monoclonal antibodies and not human-compatible monoclonal antibodies.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-4, 15-15, 24 and 41-42 are rejected under 35 U.S.C. □ 102(e) as being anticipated by June et al. (U.S. Patent No. 5,858,358; of record) (see entire document).

June et al. teach agonistic CD28-specific antibodies, including monoclonal and combinatorial antibodies and cell lines such as hybridomas that express said antibodies (see entire document, including columns 9-18) as well as the uses of said antibodies to selecting stimulate or expand T cells for use in the treatment of infectious diseases, cancer and immunotherapy (see columns 18-20).

It is noted that applicant's Remarks, filed 4/28/03 (Paper No. 25), attempts to distinguish the prior art agonistic CD28-specific antibodies from the claimed antibodies by the recitation of "activates human T lymphocytes of several to all sub-groups without being artificially crosslinked with a secondary antibody and without occupancy of an antigen receptor of the human T lymphocytes"

However, it is noted that Example 3 of the instant specification discloses that "it is not necessary to crosslink them artificially by means of a second antibody. Rather the presence of non-T cells from lymphoid organs, viz. from B lymphocytes and so-called accessory cells, is sufficient to make a direct activation by solubly added CD28-specific monoclonal antibodies possible. This probably happens through the binding of the monoclonal antibodies to so-called Fc receptors of these non-T cells. This resulted is an important precondition of the therapeutic use of directly stimulating cD28-specific monoclonal antibodies, in which an artificial crosslinking with anti-immunogloblulin antibodies in the entire organism is not practicable."

The prior art as well as the disclosed agonistic CD28-specific antibodies can act through direct activation either via crosslinking by secondary antibodies or by binding with Fc receptor expressing cells. The claimed recitation "without being artificially crosslinked with a secondary antibody" encompasses alternative methods of crosslinking or binding CD28-specific antibodies in order for said agonistic antibodies to stimulate T cells.

Given, that the prior art agonistic CD28-specific antibodies stimulated T cells via a primary activation signal or the CD3 complex such as anti-CD3 antibody (e.g. see column 5, paragraphs 1-3), the prior art CD28-specific antibodies stimulated T cells directly without occupancy of antigen receptor of human T lymphocytes (e.g T cell receptor).

Thus, the prior art agonistic CD28-specific antibodies would have had the inherent properties encompassed by the claimed products.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced products (antibodies and hybridomas).

In addition to the prior art disclosure of the uses of said antibodies to selecting stimulate or expand T cells for use in the treatment of infectious diseases, cancer and immunotherapy (see columns 18-20); it is noted that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963). See MPEP 2111.02

Also, the courts have held that if the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. In re Thorpe., 227 USPQ 964, 966 (Fed. Cir. 1985): In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983). See MPEP 2113.

Therefore, the prior art CD28-specific antibodies, including monoclonal and combinatorial antibodies and cell lines, including hybridoma anticipate the instant claims in the absence of evidence to the contrary.

As pointed out above in the rejection under 35 U.S.C. 112, second paragraph, the metes and bounds of the instant claims are ambiguous. Given the claimed limitations and ambiguous disclosure concerning the metes and bounds of the claimed "human-compatible monoclonal antibody" and "monoclonal antibody" (and the hybridomas that express said antibodies), the prior art monoclonal antibodies and combinatorial antibodies read on the instant claims. If the intent of the claims is to recite humanized antibodies, then the prior art combinatorial antibodies anticipate the claims.

9. Claims 1-4, 13-15, 24 and newly added claims 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over June et al. (U.S. Patent No. 5,858,358, of record) in view of Tacke et al. (Eur. J. Immunol. January 1997; 27:239-247, of record), and in further view of Applicant's acknowledgement on page 4 of the specification at lines 1-8 that production of hybridoma cells, humanization of antibodies, and production of monoclonal antibodies from humanized hybridoma cells was well known, as also evidenced by Bendig et al. (US Pat No. 5,558,864, of record).

The claims are drawn to human-compatible monoclonal antibodies to human CD28 which activate human T lymphocytes without occupancy of an antigen receptor (i.e., are "directly stimulating", and to hybridomas producing such antibodies.

Applicant's arguments, filed 4/28/03 (Paper No. 24, have been fully considered but have not been found convincing, essentially for the reasons of record in Paper Nos. 13/18/23 and those set forth herein.

Again, applicant's Remarks, filed 4/28/03 (Paper No. 25), attempts to distinguish the prior art agonistic CD28-specific antibodies from the claimed antibodies by the recitation of "activates human T lymphocytes of several to all sub-groups without being artificially crosslinked with a secondary antibody and without occupancy of an antigen receptor of the human T lymphocytes" and "there is no occupancy of the antigen receptor on the T lymphocyte, thus allowing it to be directly activating (see specification, page 2, lines 8-9; page 3, last paragraph and Example 3 at page 9).

However, it is noted that Example 3 of the instant specification discloses that "it is not necessary to crosslink them artificially by means of a second antibody. Rather the presence of non-T cells from lymphoid organs, viz. from B lymphocytes and so-called accessory cells, is sufficient to make a direct activation by solubly added CD28-specific monoclonal antibodies possible. This probably happens through the binding of the monoclonal antibodies to so-called Fc receptors of these non-T cells. This resulted is an important precondition of the therapeutic use of directly stimulating cD28-specific monoclonal antibodies, in which an artificial crosslinking with anti-immunoglobulin antibodies in the entire organism is not practicable."

The prior art as well as the disclosed agonistic CD28-specific antibodies can act through direct activation either via crosslinking by secondary antibodies or by binding with Fc receptor expressing cells. The claimed recitation "without being artificially crosslinked with a secondary antibody" encompasses alternative methods of crosslinking or binding CD28-specific antibodies in order for said agonistic antibodies to stimulate T cells.

Given, that the prior art agonistic CD28-specific antibodies stimulated T cells via a primary activation signal or the CD3 complex such as anti-CD3 antibody (e.g. see column 5, paragraphs 1-3), the prior art CD28-specific antibodies stimulated T cells directly without occupancy of antigen receptor of human T lymphocytes (e.g T cell receptor).

Thus, the prior art agonistic CD28-specific antibodies would have had the intrinsic or expected properties encompassed by the claimed products.

Applicant's arguments including the numerous citations to the prior art are consistent with the prior art agonistic CD28-specific antibodies that can stimulate T cells in the absence of occupying the T cell receptor, whereby the CD28-specific antibodies stimulate T cells via other primary or activation signals (e.g. PMA, anti-CD3 antibodies).

In addition to the prior art disclosure of the uses of said antibodies to selecting stimulate or expand T cells for use in the treatment of infectious diseases, cancer and immunotherapy (see columns 18-20); it is noted that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963). See MPEP 2111.02

Also, the courts have held that if the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. In re Thorpe., 227 USPQ 964, 966 (Fed. Cir. 1985): In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983). See MPEP 2113.

Therefore, the prior art CD28-specific antibodies, including monoclonal and combinatorial antibodies and cell lines, including hybridoma render obvious the instant claims in the absence of evidence to the contrary.

As pointed out above in the rejection under 35 U.S.C. 112, second paragraph, the metes and bounds of the instant claims are ambiguous. Given the claimed limitations and ambiguous disclosure concerning the metes and bounds of the claimed "human-compatible monoclonal antibody" and "monoclonal antibody" (and the hybridomas that express said antibodies), the prior art monoclonal antibodies and combinatorial antibodies read on the instant claims. If the intent of the claims is to recite humanized antibodies, then the prior art combinatorial antibodies anticipate the claims.

As pointed out previously, applicant has asserted that the Examiner admits that the anti-human CD28 antibodies of June et al. do not directly activate human T cells. However, the Examiner's comments of record were the following:

> June et al. teach antibodies to human CD28, and the production of hybridomas producing anti-human CD28 antibodies (see entire document, especially columns 5-6 and 12-17). June et al. teach that cells transfected with human CD28 can be used to immunize mice and the hybridomas producing anti-human CD28 antibodies isolated (e.g., columns 12-17). June et al. also teach that antibodies which stimulate T cell proliferation are highly desirable because they can be used to expand T cells for treatment of individuals with low numbers of T cells, as occurs in HIV infection, as well as to expand T cells for therapies requiring stimulation of an immune response (see especially columns 18-20).

The examiner did not admit that the antibodies of June et al. are not "directly stimulating", but rather observed that June et al. did not test for this activity.

With respect to the teachings of Tacke et al., the Examiner has previously observed that

> Tacke et al. teach the production of hybridomas secreting a rat antibody to human CD28 and the characterization of the rat antibody JJ316 (see entire reference, e.g., Abstract). Tacke et al. teach that the rat antibody JJ316 is specific for rat CD28 and can activate proliferation of all T cell subsets without T cell receptor occupancy (see entire document, especially Figure 2 and section 3.4). Tacke et al. also teach that the ability of the JJ316 antibody to "directly" stimulate is due to a difference in fine specificity versus other anti-CD28 antibodies that do not directly stimulate; and that antibodies with this fine specificity can be generated by immunizing with CD28 transfected cell lines more readily than by immunizing with T cells which naturally express CD28 (see especially page 245, 2nd column).

The examiner has further argued that

> [] given the teachings of Tacke et al. that directly stimulating antibodies can be produced by immunizing with a cell line transfected with human CD28, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies taught by June et al. (or to produce additional antibodies) for those monoclonal antibodies and the hybridomas producing them which are specific for human CD28 and which directly activate human T cells without occupancy of the T cell antigen receptor. One would have been motivated to screen for such antibodies and hybridomas producing them in order to derive antibodies that could be used without anti-CD3 antibodies in the methods of June et al. to expand T cells for human therapy. Given the teachings of Tacke et al. that anti-CD28 antibodies which directly stimulate T cells without occupancy of the T cell receptor are produced using immunization strategies based upon transfected cell lines rather than T cells, and the teachings of June et al. that transfected cell lines could be and were used; one of ordinary skill in the art would have had a reasonable expectation that directly stimulating antibodies specific for human

CD28 were produced or could be produces using the method of June et al. and could be identified as taught by Tacke et al.

Applicant has argued that the rejection of record constitutes an "obvious to try" rejection. However, the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 853 F.2d 894, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 444 F. 2d 433, 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ 367 (CCPA 1977); In re Lindell, 385 F. 2d 435, 155 USPQ 521 (CCPA 1967).

The examiner has previously provided a proper motivation for screening the antibodies of June et al. to identify these expected properties in order to identify antibodies that could be used without anti-CD3 to expand T cells for human therapy, as taught by June et al. The Examiner has also provided a reasonable expectation of successful isolating antibodies having the instantly recited properties because Tacke et al. teach that the instantly recited properties are expected properties of antibodies produced using transfected cells.

It is noted that the examiner has previously noted and applicant has not argued the point that

> as acknowledged by Applicant on page 4 at lines 1-8, methods of humanizing antibodies were well known in the art at the time the invention was made, as evidenced by Bendig et al. Bendig et al. also teach that human-compatible antibodies are desirable in order to reduce immunogenicity and improve antibody half-life and efficacy when administered to a human (see entire document, especially columns 21-22).
>
> It would have been obvious to the ordinary artisan at the time the invention was made to humanize the monoclonal antibodies specific for human CD28 taught by June et al., including those antibodies which directly activate T cells without occupancy of the T cell antigen receptor. Given the art-recognized methods of humanizing antibodies, as acknowledged by Applicant and as evidenced by Bendig et al., the ordinary artisan would have had a reasonable expectation of success. In addition, Bendig et al. teach that the ordinary artisan at the time the invention was made was motivated to humanize antibodies in order to produce improved therapeutics.

Further, the Examiner has previously noted and applicant has not argued the point that

> [w]ith regards to the various method steps recited in the production of the monoclonal antibodies and hybridomas, it is noted that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable

even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

10. Claims 1-4, 13-15, 24 and newly added claims 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siefken et al. (Cell. Immunol. February 1997; 176:59-65, of record), in view of applicant's acknowledgement on page 4 of the specification at lines 1-8 that production of hybridoma cells, humanization of antibodies, and production of monoclonal antibodies from humanized hybridoma cells was well known, as also evidenced by Bendig et al. (US Pat No. 5,558,864) for the reasons of record set forth in Paper Nos. 13/18/23.

Applicant's Remarks, filed 4/28/03 (Paper No. 24) do not appear to address this rejection of record.

Previous applicant's arguments have been fully considered but have not been found convincing, essentially for the reasons of record in Paper Nos. 13/18/23 and those set forth herein (see above for a discussion of how prior art agonistic CD28-specific antibodies read on the claimed limitations, particularly those drawn to applicant's attempts to distinguish the prior art agonistic CD28-specific antibodies from the claimed antibodies by the recitation of "activates human T lymphocytes of several to all sub-groups without being artificially crosslinked with a secondary antibody and without occupancy of an antigen receptor of the human T lymphocytes" and "there is no occupancy of the antigen receptor on the T lymphocyte, thus allowing it to be directly activating (see specification, page 2, lines 8-9; page 3, last paragraph and Example 3 at page 9).

Siefken et al. teach the production of hybridoma-produced antibodies to human CD28 and that the BW 828 antibody could activate human T cells without co-engagement of the T cell antigen receptor/CD3 complex (see entire document, especially "Materials and Methods" and "Discussion").

Applicant has argued that the specification distinguishes the instantly recited antibodies from those of Siefken et al. in Example 3 of the specification, which notes that unlike the antibodies of Siefken et al., the antibodies of the instant invention do not require crosslinking by means of a second antibody.

Applicant further argued that the antibodies of Siefken et al. do not stimulate "several to all subgroups" of T cells because Siefken et al. show that primarily T cells having a memory phenotype were stimulated.

However, Figure 4 shows that while memory (CD45RO+) cells certainly proliferated more readily, CD45RA+ cells also show some increase in proliferation (compare white boxes of Figure 4). Further, depending upon which "sub-group" one is considering, there are other T lymphocyte subsets encompassed within those cells that are CD45RO+. For example, one may subset CD45RO+ cells based upon their T cell receptor gene usage, chemokine receptor expression, expression of CD25, etc. The instant claims do not require any particular "sub-group" and therefore are not at present distinguished from the teachings of Siefken et al.

Siefken et al. do not teach humanization of anti-CD28 antibodies.

However, as acknowledged by applicant on page 4 at lines 1-8, methods of humanizing antibodies were well known in the art at the time the invention was made, as evidenced by Bendig et al. Bendig et al. also teach that human-compatible antibodies are desirable in order to reduce immunogenicity and improve antibody half-life and efficacy when administered to a human (see entire document, especially columns 21-22).

It would therefore have been obvious to the ordinary artisan at the time the invention was made to humanize the monoclonal antibodies specific for human CD28 taught by Siefken et al. Given the art-recognized methods of humanizing antibodies, as acknowledged by applicant and as evidenced by Bendig et al., the ordinary artisan would have had a reasonable expectation of success. In addition, Bendig et al. teach that the ordinary artisan at the time the invention was made was motivated to humanize antibodies in order to produce improved therapeutics.

With regards to the various method steps recited in the production of the monoclonal antibodies and hybridomas, it is noted that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113.

It is noted that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963). See MPEP 2111.02

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
July 10, 2003